

Testosterone Deficiency in a Man Interested in Preserving Fertility

NYU Case of the Month, November 2016

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A 53-year-old man presents with 2 years of low libido, decreased energy, and erectile dysfunction. His primary care provider ordered a serum morning total testosterone test, which was 253 ng/dL (reference range, 300-1100 ng/dL). He has two children from a previous marriage, and he and his current 34-year-old wife are interested in getting pregnant soon. He has adult-onset diabetes that is managed with metformin, and his glycated hemoglobin level is 6.1%.

Physical Examination

Physical examination reveals normal masculine hair distribution and a body mass index of 27.8 kg/m². He has no gynecomastia. His testes are bilaterally soft and approximately 14 mL in volume (normal volume \geq 18 mL). He has no varicoceles and a 30-mL benign prostate.

Evaluation

The patient was started on oral clomiphene citrate, 25 mg every other day. At 3 months, his total testosterone level increased to 531 ng/dL, his

prostate-specific antigen level was 1.6 ng/dL, his estradiol level was 29 pg/mL, and his hematocrit was 41.3%. His libido, energy, and erectile dysfunction have all improved significantly.

Comment

The physician's discussion with a patient about the risks, benefits, and alternatives of testosterone replacement therapy has become more challenging in recent years due to controversies related to cardiovascular events and clinical benefit in certain populations. However, one unequivocal adverse effect of testosterone replacement often overlooked is the negative impact of exogenous testosterone on spermatogenesis. When investigated as a male contraceptive, exogenous testosterone resulted in a complete lack of sperm in the ejaculate in nearly 75% of men after 6 months of administration. Even physicians who are cognizant of this adverse effect often make incorrect assumptions about fertility interest based on patient age. Fertility interest must be investigated as part of the evaluation of testosterone deficiency.

Test Value	Reference Range
9:30 AM total testosterone: 273 ng/dL	300-1100 ng/dL
Luteinizing hormone: 5 IU/mL	1.5-9.3 IU/mL
Follicle stimulating hormone: 3.2 IU/mL	1.6-8.0 IU/mL
Prostate specific antigen: 1.5 ng/dL	<2.5 ng/dL
Prolactin: 12.7 ng/mL	2-18.0 ng/mL
Estradiol: 18 pg/mL	<39 pg/mL
Hematocrit: 39.9%	38.5-50.0%
DEXA bone density: normal	T score > -1 SD
Semen analysis: normal	Varies by parameter

clomiphene citrate reduces the action of estradiol of the estrogen receptor, we obtain a baseline dual-energy radiographic absorptiometry scan and repeat it annually while the patient is on therapy. There are limited data suggesting that clomiphene citrate actually improves bone density over time. Additionally, estradiol levels can also increase significantly while patients are on clomiphene citrate. Again, because clomiphene citrate modulates the impact of estradiol on the estrogen receptor, it is unclear if the body is actually sensing this higher level of estradiol. Regardless, we obtain a baseline estradiol measurement, and reserve clomiphene citrate therapy for men with a ratio of testosterone to estradiol level of > 10 pg/mL. Although men on exogenous testosterone

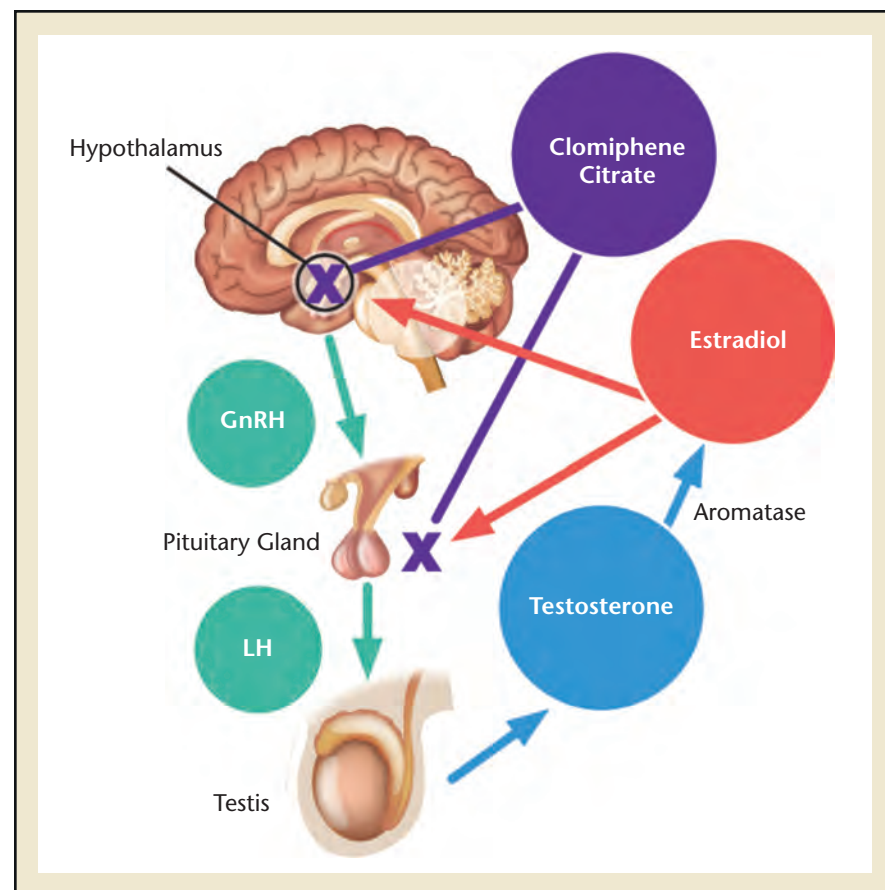
All US Food and Drug Administration–approved medications with an indication for hypogonadism negatively impact spermatogenesis. Clomiphene citrate (as an off-label treatment) is the most well-studied drug that is used to treat testosterone deficiency without negatively impacting spermatogenesis. Clomiphene citrate is a selective estrogen receptor modulator that competitively binds the estrogen receptor in the hypothalamus and pituitary gland (Figure 1). The pituitary gland senses low levels of estrogen, which is a metabolite of testosterone, through the aromatase enzyme. The effect of clomiphene citrate is to increase production of luteinizing hormone (LH), which acts on the Leydig cells in the testes to promote endogenous testosterone production.

Relatively small case series have demonstrated that clomiphene citrate increases serum testosterone to the normal range and improves symptoms of testosterone deficiency without significant adverse effects. However, the mechanism of action of clomiphene citrate requires certain modifications to a physician's process of care. Clomiphene citrate works by increasing LH secretion, so it is most effective in cases with baseline LH levels ≤ 6 IU/mL. Men who have elevated LH values are more

likely to have testicular failure, and thus may not be capable of increasing their endogenous testosterone production.

Clomiphene citrate is a selective estrogen receptor modulator, and estradiol is essential to bone maintenance in men. Because

Figure 1. Clomiphene citrate is a selective estrogen receptor modulator that competitively binds the estrogen receptor in the hypothalamus and pituitary gland. GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.



should have testosterone, hematocrit, and PSA levels monitored, men on clomiphene citrate should also have their estradiol levels monitored.

We start patients on clomiphene citrate, 25 mg every other day, and obtain follow-up laboratory values at 1 month, 3 months, and 6 months, and every 6 months thereafter. The dose is adjusted based on efficacy every 6 months, with titration up to 50 mg every other day, or 50 mg daily if necessary. When used daily,

the patient needs a 5-day hiatus every month in order to maintain efficacy.

The literature describing the safety and efficacy of clomiphene citrate in the management of testosterone deficiency is nowhere near as robust as that of exogenous testosterone. However, symptomatic patients with testosterone deficiency who have an interest in fertility preservation must not be started on any form of exogenous testosterone. Clomiphene citrate is

an important tool in the armamentarium of clinicians caring for these patients. ■

References

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